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Executive Summary

Second Annual Progress Report: Implementation of *A Public Health Action Plan to Combat Antimicrobial Resistance* *Part 1: Domestic Issues*

Interagency Task Force on Antimicrobial Resistance

June 2004

INTRODUCTION

This is the third annual progress report on implementation of *A Public Health Action Plan to Combat Antimicrobial Resistance (Part I Domestic Issues)* (1) which was released in January 2001 by the Federal Interagency Task Force on Antimicrobial Resistance. The plan provides a blueprint for federal actions to address the emerging threat of antimicrobial resistance (AR). The Task Force was formed in 1999, after hearings held by Senators Bill Frist (R - TN) and Edward Kennedy (D - MA), in recognition of the fact that addressing the multifaceted problem of AR required action by multiple agencies and departments. Co-chaired by the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the National Institutes of Health (NIH), the Task Force also includes the Agency for Healthcare Research and Quality (AHRQ), the Centers for Medicare and Medicaid Services (CMS), the Health Resources and Services Administration (HRSA), the Department of Agriculture (USDA), the Department of Defense (DoD), the Department of Veterans Affairs (DVA), the Environmental Protection Agency (EPA), and, since 2001, the US Agency for International Development (USAID).

The Action Plan was developed based on input from consultants from state and local health agencies, universities, professional societies, pharmaceutical companies, health care delivery organizations, agricultural producers, consumer groups, and other members of the public. Implementation is incremental, in collaboration with these and other partners, as resources become available. Part I of the Plan focuses on domestic issues; Part II, under development, will identify federal actions that more specifically address global AR issues in collaboration with the World Health Organization and other partners. The Task Force is continuing to meet to monitor implementation of the Plan and will release annual progress reports and seek additional input at public meetings.

This progress report contains an inventory of projects or activities that are being undertaken by the Task Force agencies to implement action items in the Plan. Like the Plan itself, this report is divided into four major sections: 1) surveillance, 2) prevention and control, 3) research, and 4) product development. The executive summary contains a brief overview of progress in implementing the top priority action items and the inventory of projects describes the status of activities for each action item. Projects applying to more than one action item in the same section are listed once and cross-referenced under the other action items in the section. Projects applying to action items in more than one section are repeated in each section.

Many projects listed in this progress report were initiated recently, after development of the Plan, and their outcome or impact cannot yet be assessed; however, such assessments are made when possible. Persons wishing more information about particular projects are encouraged to contact the responsible agency. Comments may be provided at a public meeting to be held June 30, 2004 in Bethesda Maryland (2) or submitted in writing to the pertinent agency or to: Ms. Vickie Garrett, Antimicrobial Resistance, Office of the Director, NCID, CDC, Mail stop C-12, 1600 Clifton Road, NE, Atlanta, GA 30333; telephone 404-639-2603; fax 404-639-4197; or e-mail aractionplan@cdc.gov.

SURVEILLANCE

The surveillance of drug-resistant infections requires coordination of activities by national, regional, state, and local organizations and the accurate detection of AR by clinical and public health laboratories. Because antimicrobial drug use influences the incidence and prevalence of resistance, surveillance for the extent and type of antimicrobial drug use is also needed. A national plan for surveillance of AR must include providing support to states to ensure that local needs for surveillance are met (including clinical laboratory proficiency), that surveillance is conducted for resistant organisms with a significant burden of disease or that pose especially dangerous threats to health, and that new tools are developed for detecting emerging resistance. A national plan must allow different approaches to surveillance of various organisms since it is unlikely that a single, nationwide methodology would be suitable for all pathogens in all settings, or would provide flexibility to meet local needs. However, standards and methods are being promoted that will allow comparison of data among various geographic areas and for national estimates of resistance for certain organisms.

Top Priority Action Items in this focus area include the following:

- With partners, design and implement a national AR surveillance plan that defines national, regional, state, and local surveillance activities and the roles of clinical, reference, public health, and veterinary laboratories. The plan should be consistent with local and national surveillance methodology and infrastructure that currently exist or are being developed. (Action Item #2)

- Develop and implement procedures for monitoring patterns of antimicrobial drug use in human medicine, agriculture, veterinary medicine, and consumer products. (Action Item #5)

NATIONAL SURVEILLANCE PLAN

National surveillance of AR in microorganisms that pose a threat to public health is being developed and implemented by coordinating existing projects and addressing unmet needs in collaboration with partners. Standards and methods such as the National Electronic Diseases Surveillance System (NEDSS) are being promoted in healthcare settings, large national laboratory companies, and in public health reporting by state health departments. In addition, when focused surveillance for critical pathogens is conducted, methods are being developed that can be used by state health departments and healthcare facilities not currently involved in federally-sponsored systems. Notable examples include surveillance methods for: drug resistant *Streptococcus pneumoniae* (DRSP), for which a manual is in development and a national meeting was held with state and other partners; community-associated Methicillin resistant *Staphylococcus aureus* (MRSA), for which various methods are being examined including population-based surveillance (e.g., Active Bacterial Core Surveillance project, the National Health and Nutrition Examination Surveys [NHANES]) and a national meeting was held with state and other partners; and healthcare-associated infections, for which CDC is developing the National Healthcare Safety Network (NHSN), an internet-based nationwide network that will

enhance the ability to monitor and track trends of usage and resistance of microbes to antimicrobial agents in a variety of healthcare delivery settings.

When surveillance methods have not been well established, smaller scale surveillance is being evaluated to determine appropriate standards, methods, and utility of the data. For example, for HIV resistance, CDC published results from the Sentinel Surveillance of Variant and Resistant Strains of HIV project (2).In 2003, antiretroviral resistance testing among newly diagnosed persons with HIV in the Pilot Antiretroviral Drug Resistance Testing (ARVDRT) Project began in four project areas and in 2004 17 state, local, and territorial health departments will begin antiretroviral resistance testing among newly diagnosed persons with HIV, with more areas being added in subsequent years.

For some organisms, available laboratory tests are not optimal to detect resistance (e.g., Chlamydia, trichomonas, lice). For these organisms, research is helping to develop methods of detection, and in turn, tools to conduct surveillance.

Well-established, national surveillance for drug-resistant *Mycobacterium tuberculosis* continues. This program clearly specifies activities that may be conducted at national, state, and local levels.

Standardized methods are being promoted by CDC to ensure comparability of results among geographical and institutional systems (e.g., NEDSS, cumulative antimicrobial susceptibility data). Public health officials, clinicians, and researchers are involved with many of the surveillance programs and provide for timely dissemination of data to interested parties. Necessary core capacities at state and local levels are being supported through grants (e.g., Epidemiology and Laboratory Capacity Cooperative Agreement). National AR surveillance has been built upon existing disease surveillance infrastructure. Methods and standards from current projects are either being expanded to encompass greater geographic areas or are being modified so they can be exported to areas that are not currently conducting surveillance. This is particularly true in the areas of healthcare associated infections, surveillance for *Streptococcus pneumoniae* infections, and surveillance for AR among foodborne pathogens and infections. Surveillance is also being conducted where possible through microbiology laboratories in large healthcare networks (e.g., DVA Emerging Pathogens Initiative, DoD AR Surveillance Network).

Improved surveillance for AR in agricultural settings will allow early detection of resistance trends in pathogens that pose a risk to animal and plant health, as well as in bacteria that enter the food supply. This task is being accomplished in various ways, e.g., the National Antimicrobial Resistance Monitoring System (NARMS) for Enteric Bacteria has been expanded to all 50 states and has launched a study of antimicrobial resistant pathogens found on retail foods. NARMS is a collaboration among CDC, U.S. Food and Drug Administration (Center for Veterinary Medicine) and U.S. Department of Agriculture (Food Safety and Inspection Service and Agricultural Research Services).

Surveillance data will also help improve understanding of the relationship between antimicrobial drugs and pesticides used on plants and the emergence of drug resistance. The first steps in this regard for antimicrobial pesticide products are being taken by EPA, which is reviewing current

scientific data on whether use of antimicrobial pesticide products results in the development of resistance to either the pesticide products themselves or to human or animal drugs.

Available, reliable drug susceptibility data are essential for accurate AR surveillance. Examples of activities to improve accuracy of AR detection and reporting include training and proficiency testing programs for diagnostic laboratories. CDC now has a Web site (M.A.S.T.E.R) (http://www.phppo.cdc.gov/dls/master/default.asp) which provides up-to-date information and advice on antimicrobial susceptibility testing issues in clinical microbiology laboratory practice. CDC, in collaboration with the Association of Public Health Laboratories, has published a CD-ROM that provides materials necessary for training laboratory workers to test bacterial isolates for resistance to antimicrobial agents and issue accurate reports to physicians (http://www.aphl.org/ast.cfm). CDC continues to train laboratorians through the National Laboratory Training Network. CDC is promoting and further refining standardized methods for detecting drug resistance in important pathogens, including programs for *Chlamydia*, *Mycobacterium tuberculosis*, *Streptococcus pneumoniae*, HIV and influenza. In 2002, CDC's Applied Research on Antimicrobial Resistance grant program funded projects to validate or develop breakpoints to define resistance among certain human pathogens of public health importance. Public and private sector partners have started to address barriers to AR testing and reporting, e.g., barriers due to changes in healthcare delivery.

As in the past, all surveillance activities are being conducted with respect for patient and institutional confidentiality.

MONITORING ANTIMICROBIAL DRUG USE

Methods for monitoring patterns of antimicrobial drug use are being developed and implemented as a component of the national AR surveillance plan. This information is essential for interpreting trends and variations in rates of AR, improving our understanding of the relationship between drug use and resistance, identifying and anticipating gaps in availability of existing drugs, and identifying interventions to prevent and control AR. CDC supports projects that collect data through new and existing healthcare data systems, through surveys of outpatient physicians, and through other databases (e.g., marketing surveys). The enhanced collection and electronic transfer of data on Antimicrobial Use and Resistance (AUR) component of the National Nosocomial Infections Surveillance (NNIS) allows participating hospitals to collect data that provide a national estimate of the amounts of antimicrobial agents used in these hospitals. Under the NHSN's Medication-Associated Adverse Event Module, an initial focus will be on establishing electronic reporting of antimicrobial use data. Analysis of antimicrobial use databases has proven to be complex, requiring sophisticated statistical methods and linkage with appropriate clinical information and with databases on resistant infections to be most useful. This is being done for the healthcare and community settings.

PREVENTION AND CONTROL

The prevention and control of drug-resistant infections requires measures to promote the appropriate use of antimicrobial drugs and prevent the transmission of infections (whether drug-resistant or not). Top Priority Action Items in this focus area include the following:

- Conduct a national public health education campaign to promote appropriate antimicrobial drug use as a national health priority. (Action Item #25)

- Develop and facilitate the implementation of educational and behavioral interventions that will assist clinicians in appropriate antimicrobial prescribing. (Action Item #26)

- Evaluate the effectiveness (including cost-effectiveness) of current and novel infection-control practices for healthcare and extended care settings and in the community. Promote adherence to practices proven to be effective. (Action Item #39)

- In consultation with stakeholders, finalize and implement the proposed FDA guidance and for re-evaluating currently approved veterinary antimicrobial drugs. (Action Item #58)

- Support demonstration projects to evaluate comprehensive strategies that use multiple interventions to promote appropriate drug use and reduce infection rates, in order to assess how interventions found effective in research studies can be applied routinely and most cost-effectively on a large scale. (Action Item #63)

APPROPRIATE DRUG USE

Appropriate drug-use policies are being promoted in programs targeting both the public and clinicians. AHRQ, through its network of Centers for Education and Research on Therapeutics, has sponsored education and research projects to evaluate and improve antimicrobial drug use, e.g., shared decision-making and inappropriate antibiotic use, a diagnostic decision aid for pediatric sinusitis, reducing antimicrobial prophylaxis errors, and the use of antimicrobials in acute otitis media. CDC expanded its National Campaign for Appropriate Antibiotic Use in the Community by increasing (to 26 in 2002) the number of state health departments funded to develop state-based coalitions of partners. In 2003, the campaign was renamed “Get Smart: Know When Antibiotics Work”. CDC also worked with partners (e.g., the Coalition for Affordable Quality Healthcare) to develop intervention programs for healthcare delivery organizations, developed a medical curriculum, and extended a previous focus on pediatric prescribing to adults through development of prescribing principles for upper respiratory infections and patient education materials. With the National Committee for Quality Assurance, CDC proposed two Health Plan Employer Data and Information Set (HEDIS®) performance measures for children -- Pharyngitis and upper respiratory infections – that began in 2004 (3). The DoD is developing an intervention program to enhance the communication skills of primary care providers on the prudent use of antimicrobial agents in DoD settings. The DVA has introduced guidelines and training programs regarding appropriate antimicrobial drug use for

staff and trainees in its large network of healthcare facilities. The success of programs to improve use in outpatients has been demonstrated by encouraging data from the National Ambulatory Medical Care Survey, which indicate that antibiotic prescribing rates for children seen in physician offices have declined in recent years (4).

To improve prescribing in healthcare settings, CDC launched the national campaign *Prevent Antimicrobial Resistance* in March 2002, initially focusing on hospital care of adults. This campaign involves working with partners to emphasize 12 evidence-based steps for diagnosis of infection, appropriate treatment, appropriate use of antibiotics, and prevention of infection transmission. After its initial launch, a variation of the 12-step campaign was developed for dialysis patients. Additionally, several health commuication tools were developed and disseminated to various health systems including brochures, slide sets, posters, pockets cards, and badge cards. CDC also worked with the National Committee for Clinical Laboratory Standards to develop guidelines for clinical microbiology laboratories on how to compile and report summaries of cumulative antimicrobial susceptibility data in a standardized manner to aid in clinical decisions. CMS is using the Medicare quality improvement organizations in all 50 states to promote optimal antibiotic use for inpatient pneumonia treatment and surgical infection prevention. A CMS Web-based decision support system targets improved antibiotic therapy in rural hospitals. CMS is also developing interventions to improve the use of antibiotics in long-term care facilities and physicians' offices. FDA has approved a new labeling rule intended to educate physicians and the public about the resistance problem and to encourage physicians to prescribe systemic antibacterial drugs only when clinically necessary. The Final Labeling Rule was published in the Federal Register on February 6, 2003, and the rule will go into effect February 6, 2004.

PREVENTING INFECTION TRANSMISSION

Widespread use of a new pneumococcal vaccine for children was temporally associated with unprecedented declines in cases of invasive pneumococcal disease and in the proportion of cases resistant to antimicrobial drugs. CDC data from ongoing population-based surveillance of invasive pneumococcal disease in 7 geographic areas indicate that the number of cases in children under 2 years of age declined by 75% in 2002 (compared with data from 1998 and 1999). Vaccination also reduced the racial disparity in disease rates, with rates for both white and black children falling below the Healthy People 2010 target of 46 cases/100,000 population. The number of cases of invasive disease in adults also declined, suggesting that vaccine use may have helped to decrease transmission of pneumococci to unvaccinated persons. Five of the seven-pneumococcal serotypes in the vaccine account for most of the pneumococcal strains that are resistant to penicillin and other antibiotics. The rate of disease caused by strains that were not susceptible to penicillin was 51% lower in 2002 than 1999. (5)
In 2003, the public sector purchased 56% of the national vaccine supply for childhood supply through a combination of federal and state/local funding. CDC provides funds and technical assistance to 64 state, territorial, and local health departments for immunization programs.
CMS promotes and pays for pneumococcal and influenza vaccination of Medicare beneficiaries. CMS's ongoing Healthy People 2010 has a goal of increasing targeted adult immunization rates to 90%. The campaign is funded and focused on improving immunization rates among minorities and other vulnerable populations.

The effectiveness of current and novel infection control practices is being evaluated in CDC's network of Centers of Excellence in Healthcare Epidemiology, a program in which prevention research to improve infection control practices is conducted at 7 academic medical centers. Infection control is also a major element of the campaign *Prevent Antimicrobial Resistance*, outlined above, and of the comprehensive demonstration programs outlined below. DVA has an ongoing program to evaluate the outcome of infection control interventions for serious infectious diseases. Improved infection control practices reduce the spread of infections in healthcare settings and thus also decrease the use antimicrobial drugs.

FDA REGULATORY FRAMEWORK FOR ANTIMICROBIAL DRUGS IN FOOD ANIMAL PRODUCTION

A regulatory framework for antimicrobial drugs used in food-animal production, proposed by FDA, was discussed extensively with stakeholders, and the concepts were refined on the basis of comments received. A draft guidance document for industry incorporating these changes was published in September 2002 and a public meeting held October 2, 2002 to explain the guidance and solicit additional comments. An approach for evaluation of drugs according to their importance in human medicine has been incorporated into the pre-approval assessment strategy and is fully explained in the draft guidance document. That portion of the document was taken to a FDA Anti-Infective Drugs Advisory Committee in January 2003. Comments from the advisory committee as well as comments received at the public meeting in October and all written comments have been evaluated. The FDA published the final guidance document titled "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern" (6) in October 2003. This document outlines a pathway drug sponsors can use to address concerns about antimicrobial resistance prior to approval of their drug. The guidance balances the need for antimicrobials to treat livestock and poultry with the need to protect human health by considering the importance of drugs in human medicine.

The document applies to therapeutic and non-therapeutic antimicrobial drugs intended for use in food-producing animals. It will also lead to a review of all existing approvals; review of the penicillin products approved for growth-promotion uses has recently been completed. The guidance document process uses a qualitative risk assessment approach to assess the potential of the intended use of a product to develop resistance in bacteria that may harm humans. The level of risk determines the level of risk management that is required for the drug to be used. FDA has the option of not approving a drug if the risk of a public health consequence is too high.

An analysis (risk assessment) of the relationship between the emergence of quinupristin-dalfopristin resistant *Enterococcus faecium* in humans and the use of virginiamycin in food animals will soon be published in draft. A risk assessment of the use of fluoroquinolones in poultry was completed; given its conclusions, the Center for Veterinary Medicine proposed withdrawing approval of fluoroquinolones for use in poultry. One of the two affected drug manufacturers withdrew its fluoroquinolone product, and the other requested a hearing which is in progress. The Administrative Law Judge filed an initial decision in early 2004 agreeing with the Center for Veterinary Medicine and stating that the poultry fluoroquinolone product should be removed from the market. Bayer has appealed this decision.

COMPREHENSIVE DEMONSTRATION PROJECTS

Comprehensive demonstration projects involving a wide variety of nonfederal partners were implemented to prevent and control AR through multiple interventions (e.g., surveillance, appropriate drug use, optimized diagnostic testing, immunization practices, and infection control). CDC-sponsored projects included a regional approach involving a coalition of healthcare facilities and business and community leaders in Pittsburgh, a statewide program in Wisconsin, a group of healthcare institutions in Chicago, and an integrated approach in rural communities in Utah and Idaho. The success of comprehensive regional approaches such as these is illustrated by the control of vancomycin-resistant enterococci in the Sioux City, Iowa area, with leadership from the Sioux City Health Department and support from the Iowa, South Dakota, and Nebraska State Health Departments, and CDC. (7)

RESEARCH

Knowledge and understanding of the growing problem of antimicrobial resistance (AR) is a prerequisite for a planned and coordinated federal response to this challenge. Numerous federal agencies are engaged in developing the scientific base of knowledge through support and conduct of bench, applied, and clinical research. The NIH has the lead in this area, but increasingly the federal agencies are collaborating and pooling resources to accomplish the action items within this chapter. Research accomplishments in the following areas will be highlighted in this executive summary:

- Supporting additional research, including high risk and high payoff research in nontraditional fields that will lead to an increased understanding broadly of: microbial physiology, ecology, genetics, mechanisms of resistance, host factors; and the impact of variable antimicrobial use patterns, preventive, therapeutic, and growth promoting agents, and environmental residues on the emergence and spread of resistant organisms and resistance factors. (Action Item #67)

- Providing to the research community genomics and other powerful technologies to identify targets in critical areas for the development of new rapid diagnostics methodologies, novel therapeutics, and interventions to prevent the emergence and spread of resistant pathogens. (Action Item #70)

- Work with the appropriate peer review structures to ensure that the requisite expertise is applied to the review process to facilitate funding of quality ar research. (Action Item #69)

- In consultation with academia and the private sector, identify and conduct human clinical studies addressing AR issues of public health significance that are unlikely to be studied in the private sector. (Action Item #75)

- Encouraging basic and clinical research in support of novel approaches to preventing or treating infections with resistant organisms that occur in humans and animals by partnering with academia and the private sector. (Action Item #78)

EXPANDING THE RESEARCH BASE

Over the past year, ongoing and new initiatives have extended grant and funding opportunities related to or including antimicrobial resistance to new groups and investigators and are stimulating research in this area. Representative initiatives include basic, applied, and product-oriented research areas and have been directed at academicians and industrial researchers. The Small Research Grant and the Exploratory/Developmental Research Grant announcements listed in the 2003 Annual Report have begun to result in funded awards focused on antimicrobial resistance and drug development. These funding mechanisms join the long-standing investigator-initiated R01 mechanism and the Small Business Innovation Research award mechanisms in providing meaningful platforms for advancing antimicrobial drug development and resistance research as evidenced by an accumulating spectrum of funded projects. The cumulative listing of funded awards can be searched at http://crisp.cit.nih.gov/ using various key words of interest.

The NIH continued to encourage solicitations involving partnering with the industrial sector in 2003 through the "Cooperative Research for the Development of Vaccines, Adjuvants, Therapeutics, Immunotherapeutics, and Diagnostics for Biodefense and SARS" and the "Challenge Grants: Biodefense and SARS Product Development" initiatives. While the focus was on specified pathogens such as Category A, B, or C pathogens of relevance to Biodefense and SARS, it is clear that antimicrobial development projects hold great promise to extend the number of available antimicrobial drug candidates when compounds under study have broad spectrum of action against multiple microorganisms. Also, it is anticipated that the knowledge gained from advancing diagnostic and vaccination approaches to the target organisms will have benefit to these disciplines overall.

The CDC has expanded its extramural grants program to address antimicrobial resistance in each of the past two years. Additionally, the 2003 Annual Report highlights a number of USDA antimicrobial resistance and microbial ecology projects to exemplify the breadth of federal coverage of the research topic of antimicrobial resistance in commensal bacteria in livestock and in the food supply.

SCIENCE AND TECHNOLOGY SUPPORT

The NIH and other federal agencies have made a significant investment in the sequencing of whole pathogen genomes. Coordination of these numerous activities across federal agencies occurs through the Microbe Project Interagency Working Group including NIH, USDA, NSF, DOE, DOD and FDA. The ultimate goal is to foster the burgeoning field of pathogen genomics which, supported by the development of various new technologies, continues to uncover clues to microbial functioning that hold promise for the prediction of disease progression and for patient care and treatment, ultimately translating genomic information into clinical applications. In FY2003, NIAID supported approximately 40 large scale DNA sequencing genome projects for microbial pathogens and invertebrate vectors of infectious diseases, including new projects for

Burkholderia thailandensis, different strains of *Bacillus anthracis*, another strain of *Bacillus cereus*, and another strain of *Clostridium perfringens*. Genome sequencing projects for *Burkholderia mallei*, *Clostridium perfringens*, *Escherichia coli (K1 RS218)*, *Rickettsia rickettsii*, *Rickettsia typhi*, *Salmonella typhi*, *Streptococcus agalactiae* and Wolbachia were completed. In addition, DNA sequencing projects have been completed for parasites *Cryptosporidium parvum* (bovine isolate). *Leishmania major*, and *Trypanosoma cruzi* In total, NIAID-investigators have completed 42 genome sequencing projects for 37 bacteria, 4 parasitic protozoa, and 1 invertebrate vector of infectious disease.

Over the past year NIH's Pathogen Functional Genomic Resource Center has provided microarray slides, computational tools, and training to researchers to study organisms that pose important public health challenges. Functional genomics research reagents are available or are in development for *Staphylococcus aureus, Salmonella typhimurium, Streptococcus pneumoniae,* Group B *Streptococcus agalactiae, Trypanosoma brucei, Helicobacter pylori, Aspergillus fumigatus, Trypanosoma cruzi, Mycobacterium smegmatis, Streptococcus mutans, Porphyromonas gingivalis, Bacillus anthracis, Yersinia pestis, Vibrio cholerae, Clostridium botulinum, Listeria monocytogenes*, and selected Corona viruses.

These activities have accelerated our understanding of the genetic basis of antimicrobial resistance in these and other pathogens. The functional analysis of genes and proteins in whole organisms and cells being carried out through federally supported research projects, combined with the availability of the human genome, advances our understanding of host pathogen interactions and affords opportunities to impact disease causing processes.

PEER REVIEW STRUCTURES

NIH's Center for Scientific Review (CSR) has established a new Study Section, Drug Discovery and Mechanisms of Antimicrobial Resistance (DDR), within the new Infectious Diseases and Microbiology Integrated Review Group (IRG). It will review grant applications that are concerned with the identification of novel antimicrobial agents, including agents that could be used in bioterrorism, for the prevention and treatment of infectious diseases and the study of the evolution, mechanisms, and transmission of resistance. NIH CSR reviews applications for multiple federal agencies sponsoring research programs.

IDENTIFY AND CONDUCT HUMAN CLINICAL STUDIES ADDRESSING AR ISSUES OF PUBLIC HEALTH SIGNIFICANCE

The NIH Bacteriology and Mycology Study Group and associated Bacteriology and Mycology Biostatistical and Operations Unit continue to support clinical trials involving fungal and resistant bacterial infections. A reserve fund to support orphan studies that cannot be funded through industrial sponsors is available through the BAMSG contract. This fund will enable the group to undertake more independent, innovative, and public health-oriented clinical studies. Concepts have been approved and protocols are under development for two studies addressing antibacterial resistance: (1) "Infection control strategies to reduce colonization and infection caused by antimicrobial-resistant bacteria in an adult intensive care unit;" planned to begin in August 2004; and (2) "Randomized, multicenter, comparative trial of short-course course

antibiotic therapy vs. standard therapy with patients with pulmonary infiltrates in the intensive care unit;" enrollment planned for Dec 2004.

NOVEL THERAPEUTIC AND PREVENTIVE APPROACHES

Research partnerships are advancing the development and testing of novel products to address resistant pathogens, such as *Mycobacterium tuberculosis*. Tuberculosis has a major impact on health through out the world, with the emergence of resistance seriously complicating therapy. The NIH supports research on mechanisms of drug resistance and activity, early target identification and verification, and clinical testing of prophylactic and therapeutic anti-TB regimens. The Global Alliance for TB Drug Development, with CDC, NIH and USAID as partners and over 30 stakeholder organizations involved, is stimulating new drug development for TB. Promising compounds are under development. Other potential compounds with promise as TB drugs are being screened through a variety of NIH contracts and collaborations. In addition, the search for new antimicrobials in unusual settings is being carried out through the International Cooperative Biodiversity Groups Program in collaboration with the other components of the NIH, the National Science Foundation and the USDA. Six awards have been made to multidisciplinary research groups that also include in-country researchers, to explore natural products as a source of pharmaceuticals. Through these activities and others described in the Task Force Inventory of Projects, NIH and the other federal partners are investing in target discovery and moving promising products down the developmental pathway.

PRODUCT DEVELOPMENT

New products must keep pace with the development of pathogens resistant to currently available antimicrobials. We need to foster the development of new classes of antimicrobial agents that are effective against resistant organisms. We also need to develop vaccines and anti-infective devices with the potential to prevent infections. In addition, the development of improved diagnostic tools is needed to aid in the appropriate use of therapeutic agents.

Product development is also an important issue for veterinary medicine and agriculture. U.S. agencies and private sector partners must intensify efforts to encourage the development and use of veterinary drugs and agricultural practices that are unlikely to stimulate resistance to important human drugs or spread resistant pathogens to humans. In addition, we need to focus attention on developing strategies to prevent animal infections (e.g., vaccines, changes in husbandry).

Pertinent issues include:

- Researchers and manufacturers need to be better informed of current and projected gaps in the arsenal of antimicrobial drugs, vaccines, and diagnostics and of potential markets for these products.

- Market incentives and regulatory processes need to be adequate to stimulate the development of AR products while promoting the appropriate use of new and currently available agents.

- The development and use of antimicrobial drugs and related products in agriculture and veterinary medicine need to be optimized to reduce the development and transfer of resistance to pathogens that can infect animals and humans.

Top priority action items in this focus area include:

- Use the existing mechanisms of FDA advisory committees and workshops to identify and publicize priority public health needs in human and animal medicine for new AR products. (Action Item #79)

- Identify ways to promote the development and/or appropriate use of AR products, such as novel compounds and approaches, for human and veterinary medicine for which market incentives are inadequate. (Action Item #80)

ASSESSMENT OF FUTURE NEEDS FOR AR PRODUCTS

To provide a systematic assessment of the current status and projected future needs for AR products, a cooperative interagency effort involving stakeholders including regulated industry is intended to identify and publicize priority public health needs in human and animal medicine for new AR products. FDA has chosen to perform these cooperative activities within an existing framework (i.e., pre-existing advisory committees) and co-sponsored workshops with other stakeholders to enhance the efficiency and the applicability of the results of such discussions. FDA has begun this process through the following ongoing activities:

- Determine which resistant pathogens are of the greatest public health importance in terms of multidrug resistance and for which there are few available therapies.

- Identify current areas/anticipate future areas of greatest need for drug development.

- Consider and assess proposed resistant pathogen claims for product labeling

- Address clinical design issues in acute otitis media, acute bacterial sinusitis, and acute exacerbations of chronic bronchitis, and other indications in attempts to streamline drug development through higher quality data.

- Consider the perspectives of experts from a range of disciplines on issues such as modeling future resistance trends, identifying product needs and potential markets, considering appropriate AR surveillance data and numbers of patients at high risk of developing drug resistant infections.

- Address issues of incentives and disincentives for developing AR products.

- Reassess AR product priorities regularly.

- Evaluate the availability of currently approved, critical products for drug resistant infections when shortages or the potential for shortages exists and develop strategies to ensure that the supply of these products meet public health needs.

- Coordinate information and priorities developed through cooperative efforts with other agencies and stakeholders to further advance action efforts in research, prevention and control, and product development.

- Consider government's role in the discovery of drugs and other products targeted to address areas in which market incentives are limited and unmet needs exist. This role could use intramural, extramural or partnership-type mechanisms. The products developed under such mechanisms could be licensed commercially either with or without specific stipulations about use.

PROMOTING DEVELOPMENT OF AR PRODUCTS

FDA is developing guidance on the development of antimicrobial drugs for diseases due to infections with resistant pathogens. FDA has held meetings with industry stakeholders, and made presentations at numerous scientific and public advisory committee meetings. FDA is also developing guidance documents to promote the development of novel types of AR products (e.g., topical antimicrobicides, plant-based vaccines). Finally, FDA is considering additional incentives beyond existing regulatory tools to further stimulate AR drug development. Future plans include:

- Consult with outside stakeholders to explore potential pilot programs that may stimulate antimicrobial drug development.
- Consult with other government agencies on programs that may encourage antimicrobial drug development

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